PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	Docket No: **Q80490**
Kazunari YAMAGUCHI *et al.*	Conf. No.: **9623**
Appln. No.: **10/805,220**	Group Art Unit: **1648**
Filed: **March 22, 2004**	Examiner: **Chen, Stacy**

For: **METHOD FOR DETECTING BORNA DISEASE VIRUS INFECTION**

REPLY BRIEF PURSUANT TO 37 C.F.R. § 41.41

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the provisions of 37 C.F.R. § 41.41, Appellants respectfully submit this Reply Brief in response to the Examiner's Answer dated July 30, 2009. Entry of this Reply Brief is respectfully requested.

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I. STATUS OF CLAIMS

Claims 17, 24, 26 are pending in the application. Claims 1-16, 18-19, 20-23 and 25 are cancelled. All pending claims are currently rejected. This reply is directed to rejected claims 17, 24 and 26.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole ground of rejection on appeal is whether the Examiner erred in rejecting claims 17, 24 and 26 under 35 U.S.C. § 103(a) as being unpatentable over Yamaguchi *et al.* (*Ann. Clin. Biochem.* 2001, 38:348-355), in view of Watanabe *et al.* (*J. Vet. Med. Sci.*, 2000, 62(7):775-778,), Planz *et al.* (*Journal of Virology*, 1999, 73:6251-6256) and further in view of Hatalski *et al.* (*Journal of Virology*, February 1995, 69(2):741-747), and Carbone, K.M. (*Clin. Micro. Rev.*, 2001, 14(3):513-527).

III. ARGUMENT - FORMALITIES

A. Compaction of Prosecution is Respectfully Requested

It is incumbent on the Office to furnish Appellants with an Examiner's Answer in response to Appellants' Brief within 2 months after receipt of the Brief by the Office. MPEP § 1207.02. Appellants respectfully request timely future notice to compact prosecution and appeal.

B. The Examiner's Answer is Improper Under MPEP § 1207.02 (A)(9)

In order to clarify the record for appeal and to most precisely present the arguments, MPEP § 1207.02 (A)(9) indicates,

> "(e) For each rejection under 35 U.S.C. 102 or 103 where there are questions as to how limitations in the claims correspond to features in the prior art even after the examiner complies with the requirements of paragraphs (c) and (d) of this section, the examiner *>must< compare at least one of the rejected claims feature by feature with the prior art relied on in the rejection. The comparison *>must< align the language of the claim side-by-side with a reference to the specific page, line number, drawing reference number, and quotation from the prior art, as appropriate."

The Examiner's Answer fails to comply with MPEP § 1207.02 (A)(9)(e). Correction of the Examiner's Answer is respectfully requested (*e.g.*, the Office fails to explain how the viral proteins in the cited references are equivalent to the synthetic peptides for purposes of this assay).

III. ARGUMENT - REPLIES

The Examiner erred in rejecting claims 17, 24 and 26 under 35 U.S.C. § 103(a) over Yamaguchi *et al.* in view of Watanabe *et al.*, Planz *et al.*, Hatalski *et al.*, and Carbone. The

Examiner's Answer dated July 30, 2009 fails to remedy the errors made in rejecting claims 17, 24 and 26 under 35 U.S.C. § 103(a). Appellants respectfully request the Board to reverse the obviousness rejection for the reasons set forth in Appellants' Appeal Brief for at least the following reasons.

A. The References Cited By The Office Fail To Teach Or Suggest Appellants' Methods Claimed in Claims 17, 24 and 26 - There Is No Motivation To Combine

At page 6 of the Examiner's Answer, in response to the arguments set forth in Section A (pages 9-12) of Appellants' Appeal Brief, the Examiner asserts several rebuttal arguments. Appellants' response is as follows.

In response to Appellants' specific argument - that the combined teachings of Watanabe *et al.*, Hatalski *et al.* and Carbone fail to provide a requisite motivation to modify Yamaguchi *et al.*'s ECLIA method to include synthetic p10 peptides or p10 antibodies and fail to provide the motivation to examine both IgM and IgG antibodies in Appellants' assay - the Examiner asserts that *explicit* reference to motivation is unnecessary. The Office admits that an *explicit* motivation to combine the elements of the cited prior art references to render obvious Appellants' invention has not been identified.

The Office asserts that the rationale for combining the elements disclosed by the references is increasing "the sensitivity of Yamaguchi's method" and that this rationale motivates one to add synthetic p10 to arrive at Appellants' invention. According to the Examiner, this rationale is supported by the *Graham* factual finding that "Wantanabe suggests

that antibodies to individual viral proteins and BDV-specific antigens are useful for establishing diagnostic methods (page 777, second column, last paragraph)" and by "the fact that Wantanabe found anti-p10, anti-p24 and anti-p40 antibodies in serum at the same time (Wantanabe, abstract)". But Wantanabe *et al.* does not state these facts.

Watanabe *et al.* does not state that antibodies to individual viral proteins and BDV-specific antigens are useful for establishing diagnostic methods. Rather, Watanabe *et al.* prophetically states, "the results in this study *could be worthy* for establishment of diagnostics method for BDV infection." [Emphasis added] Watanabe, page 777, column 2.

Further, there is no teaching or suggestion that adding a third synthetic peptide would increase the sensitivity of a BDV diagnostic assay. Appellants have pointed out, one having ordinary skill understands based on the scientific evidence of record that adding additional BDV antigens in a diagnostic method could compromise the specificity of the assay unless the antigen is carefully selected by examining its expression profile and the cross reactivity of the antibody raised against the antigen.[1] Thus, it is not common sense nor a rational underpinning that mere

[1] As previously asserted by Appellants (e.g., Appellants' Appeal Brief, page 14), the record reflects that Appellants pointed out, and the Office failed to rebut, that the validity of a diagnostic test can be determined by measuring the rate of sensitivity (true-negative rate) and specificity (true-positive rate) (Carbone *et al.*, Page 515, Column 2, line 47-50) thus, it is equally important to improve the specificity of diagnostic tests in order to minimize false positives to prevent unnecessary treatment. Additionally, Appellants pointed out that BDV expresses 6 classes of proteins (N,P,M,G,L, and p10) which undergo distinct secondary modifications (i.e., glycosylation and phosphorylation) and that the viral proteins form distinct heteromeric complexes (Carbone *et al.*, Page 514, Column 1, line 27-31). *See* Amendment Under 37 C.F.R. § 1.116, December 19, 2008, page 8. Thus, contrary to the Office's assertion at page 10 of the Examiner's Answer that Appellants' have provided no evidence to support their arguments, Appellants' evidence is of record and remains unrebutted by the Office.

mention of BDV viral proteins is tantamount to a motivation to include any number of synthetic peptides in an assay for BDV detection, let alone specifically including synthetic p10.

Accordingly, the combined teachings of Watanabe *et al.*, Hatalski *et al.* and Carbone, in view of the knowledge in the art, fail to provide the motivation to modify Yamaguchi *et al.*'s ECLIA method to include synthetic p10 peptides or p10 antibodies.

The lack of motivation to assay for both IgM and IgG antibodies is addressed below in Section B.

B(1). The Office Fails To Set Forth A Reason Supported By A Rational Underpinning That Would Have Prompted One Of Ordinary Skill To Combine The Elements The Way Appellants' Invention Does

At pages 7 to 10 of the Examiner's Answer, the Office admits that the Examiner's obviousness analysis is a reconstruction based on hindsight reasoning but the Office asserts that the analysis does not include knowledge gleaned only from Applicants' disclosure. Appellants respectfully disagree.

There is no suggestion to combine Yamaguchi *et al.*'s assay to include detection of synthetic peptide p10 corresponding to SEQ ID NO:8 except from using Appellants' invention as a template through a hindsight reconstruction of Appellants' claims. Further, Appellants' Brief (e.g., page 15) explains that the Office's use of improper hindsight in making the rejection is made more apparent in light of the scientific facts in Yamaguchi *et al.* Yamaguchi *et al.* underscores the difficulty in diagnosis of BDV infection. Yamaguchi *et al.* state, "IFA does not

always give definite results, due to the existence of cell specific auto-antibodies, the variability of subjective interpretation, and insufficient sensitivity in detecting low titer antibodies." Yamaguchi *et al.*, page 349, column 1. The reference states, "although IP and WB analyses may be more reliable and specific than IFA, these methods are time consuming and expensive and therefore unsuitable for large-scale screening." Yamaguchi *et al.*, page 349, column 1. Despite the scientific evidence of record, at page 9 of the Examiner's Answer, the Office asserts, "multiple antigen/antibody detection in the art of BVD assay is commonly practiced, evidenced by Yamaguchi and Wantanabe." This statement is plainly contrary to the unrebutted scientific evidence of record which is summarized in detail, *inter alia*, at pages 16-21 of Appellants' Appeal Brief and below, in Section B(2).

Regarding Hatalski *et al.* and Carbone, neither reference teaches or suggests detecting IgM and/or IgG following BDV infection. Carbone refers to detection of anti-BDV IgG antibodies at the convalescent-phase. It is known in the art that IgM antibodies are the first class of antibodies that are made in response to infection. Carbone, page 516, Column 1, line 27-30. However, one of skill knows that most IgM antibodies quickly disappear, approximately one month after their appearance, and are replaced by IgG antibodies. Specification, page 2, first paragraph. Thus, the detection of IgG antibodies alone is known in determining infection by BDV since at the relevant time frame IgM antibodies were understood to be absent. In addition, Carbone states (and one having ordinary skill would understand based on the scientific evidence of record) that it is unlikely to obtain acute phase serum in natural BDV infections. Carbone, page 516, column 1, line 37-40. This evidence is unrebutted by the Office. Despite this

evidence, the Office maintains, without scientific evidence, that IgM and/or IgG would have worked in Yamaguchi *et al.*'s method and, because both antibodies would have worked Appellants' invention is obvious. The Office alleges, "if one does not know the stage of infection, one would be motivated to increase the sensitivity of Yamaguchi's assay to detect any possible markers of an infection at any stage", even though Carbone states it is unlikely to obtain acute phase serum in BDV infections. Carbone, page 516, column 1, line 37-40.

There is no suggestion to combine Yamaguchi *et al.*'s assay to detect IgM and IgG except from employing, as the Office has done, impermissible hindsight from knowledge gleaned from Appellants' specification. Because speculation cannot substitute for a reason, supported by *Graham* facts, that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does, and because hindsight alone was employed in the obviousness analysis, the rejection should be withdrawn.

B(2). The Office Failed To Appreciate Numerous Teachings Away From Appellants' Claims 17, 24 and 26

At pages 11 to 13, the Office now admits that Appellants' arguments in Section B2 of Appellants' Appeal Brief (pages 16-21) are correct indicating,

> **"the Office recognizes that the art as a whole acknowledges that the acute phase and persistent stages of BDV infection are difficult to determine based on antibody detection using IFA methods."**

However, the Office appears to assert that the scientific evidence is insufficient to establish unpredictability in the art of BDV diagnosis because the arguments "are not evidence of no expectation of success." [Emphasis added] The Office is incorrect on the science and the law.

A rationale to support a conclusion that a claim is obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements, as claimed, by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). Faced with the scientific evidence of record the Office had no choice but to admit that BDV diagnosis was unpredictable in the relevant time frame.[2] Taken together, the Examiner's admission and the evidence contained in the cited references clearly indicate that due to the unpredictable nature of BDV detection the law and Office Guidelines were not properly applied in making the obviousness rejection because the unpredictable nature of BDV detection was accorded no weight in the obviousness analysis. Predictability is a key determinant in an obviousness analysis, particularly in an unpredictable art such as BDV detection thus, the Office must accord proper weight to this evidence. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

[2] The Office's admission is now consistent with the position of unpredictability asserted, e.g., at pages 4 to 5 of the Office Action dated November 30, 2007, wherein in making a lack of enablement rejection the Office argued, "the state of the art also speaks to the low level of predictability in the art..."

At page 12 to 13 of the Examiner's Answer, the Office asserts that the numerous instances of teaching away pointed out by Appellants are not evidence and that Planz *et al.* "does not teach that antibodies to BDV are never present." Appellants respectfully disagree.

A reference teaches away when a person of ordinary skill in the art, upon reading the information in the reference, would be discouraged from following the path set out in the reference, or would be led in a path divergent from the path taken by Appellants. See *Monarch Knitting Mach. Corp v. Sulzer Morat Gmbh*, 139 F.3d, 877, 45 USPQ2d 1977 (Fed. Cir. 1998); *Para-Ordnance Mfg. v. SGS Importers Int'l Inc.*, 73 F.3d1085, 37 USPQ2d 1237 (Fed. Cir. 1995); and *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). "[W]hen the prior art teaches away from the claimed solution...obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition." [Emphasis added] *Ex parte Whalen* (Bd. Pat. App. & Int., July 23, 2008). Thus, a "teaching away" is any information that indicates that the elements proposed by the Examiner would not be combined.

Appellants presented numerous teaching away evidence (Appellants' Brief, pages 21 to 24) however, the Examiner dismissed the evidence without directly rebutting the cited facts or properly according the evidence weight. At page 13 of the Examiner's Answer, the Examiner indicates, "Yamaguchi did not state that p24 and p40 were the only markers ever to be used for BDV detection" [emphasis added] but, absolute statements are not the proper legal standard for

assessing and applying teaching away evidence. A reference teaches away when a person of ordinary skill in the art is discouraged or led in a path divergent from the path taken by the Appellants. The library of references cited by the Office makes clear that a person of ordinary skill in the art, upon reading the references, would be led down a different path from the path taken by Appellants (i.e., would not include synthetic antigens other than p24 and p40 in a BDV diagnostic method because BDV detection was already reported in peer reviewed scientific literature to be perfected). Appellants' Brief, pages 21 to 24. In view of the scientific evidence in the references, Appellants' method is non-obvious and the rejection should be withdrawn.

The Examiner's statement that Planz *et al.* "does not teach that antibodies to BDV are never present" is curious in view of the reference. For example, the Office has again overlooked significant passages of Planz *et al.* - "sera were obtained from all three patients and tested either in Western blot analysis or by immunofluorescence for the presence of BDV specific antibodies" and "interestingly, in these sera, no virus specific antibodies could be detected, even at dilutions of 1:2 in immunofluorescence." [Emphasis added] Planz *et al.*, page 6255, first column, first paragraph. The title of the paper alone rebuts the Examiner's position indicating infection of the granulocyte fraction absent antibodies. The observations in Planz *et al.* are plainly contrary to the Examiner's conclusion of obviousness.

The library of references cited by the Office makes clear that a person of ordinary skill in the art, upon reading the reference, would be led down a different path from the path taken by Appellants. In view of the information in the references, Appellants' method is non-obvious and the rejection should be withdrawn.

C. The Office Failed To Appreciate Appellants' Unexpected Superior Results of the Methods of Claims 17, 24 and 26

At page 14 of the Examiner's Answer (referencing the remarks made in Second Section B, at pages 12 and 13 of Appellants' Appeal Brief), the Office asserts that Appellants' unexpectedly superior results are not unexpected because "the increased detection of BDV in the assay that detected p10, p24 and p40 is not surprising because the sensitivity of the assay was increased." Absent reliance on *post hoc ergo propter hoc,* the Examiner provides no analysis of the experimental results pointed out by the Appellants. Appellants respectfully disagree with the Examiner.

The instant specification discloses unexpected results. As indicated at pages 24 to 26 of Appellants' Appeal Brief, one unexpectedly superior result is based on the unexpected appreciation that it requires an unusually long period of time for antibody class switching (i.e., going from IgM to IgG) to occur when antibodies to BDV are made (Page 31, line 1-4). Appellants demonstrate that IgM antibodies are detected even one year after BDV infection (page 12, line 17-22). Thus, the unexpected property of the IgM antibodies disclosed by Appellants allows one to examine the presence of both IgM and IgG not only at the early phase but also at the later phase of BDV infection. One of ordinary skill in the art would not have had a reasonable expectation that testing both IgM and IgG antibodies would increase the sensitivity in detecting an infection absent the knowledge gleaned from Appellants' disclosure.

Appellants again acknowledge that it might be difficult to determine if a subject is actively or latently infected with BDV based upon the detection of the antibodies as disclosed in the present invention. However, contrary to the Examiner's assertion, the objective of the present invention is not determining whether a subject is in an active or a cleared state of BDV infection. Rather, the present invention is directed to "a method for detecting whether a subject has been infected with Borna Disease Virus" as recited in Claims 17, 24 and 26.

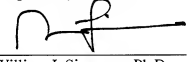
Further, Appellants submit that the present invention provides unexpectedly superior results over Yamaguchi *et al.*'s ECLIA method, the Office's primary reference. Comparative Example 1 of the specification demonstrates improvement of BDV detection rate when p10 antibodies are included in the assay in comparison to the method detecting p24 and p40 antigens, e.g., Yamaguchi *et al.* (pages 22-25, Table 1). Specifically, Table 1 shows that 17 out of 23 specimens (73.9%) are detected as positive for BDV infection when p24 and p40 antibodies are used in the assay. In contrast, the data show that the BDV detection rate increases to 95.7% (22 out of 23 specimens) when p10 antibodies are included in the method. Importantly, 5 out of 23 specimens were detected with p10 antibodies but <u>not</u> with p24 nor with p40 antibodies indicating that the detection of p10 increases the sensitivity of the BDV detection method <u>without</u> compromising the specificity of the assay. The Examiner fails to address this evidence in the Examiner's Answer but rather summarily dismisses the results blindly concluding that adding any antigen to an assay increases sensitivity - an unsupported overly simplistic interpretation of the art that is contrary to the scientific evidence of record (i.e., see, *inter alia*, Section B2 rebuttal arguments and pages 16 to 21 herein and in Appellants' Brief, respectively).

Together, the information in the references relied on by the Examiner would not have and could not have led one of ordinary skill in the art to achieve the subject matter of claims 17, 24 and 26. The combined teachings of Watanabe *et al.*, Hatalski *et al.* and Carbone fail to provide a motivation to modify Yamaguchi *et al.*'s ECLIA method to include the p10 antibody and to examine both IgM and IgG antibodies in the assay and in fact teach away from such a combination. Furthermore, Appellants submit that the present invention demonstrates unexpected superior results over Yamaguchi *et al.*'s method.

CONCLUSION

Accordingly, in view of foregoing, Appellants submits that the present invention is not obvious over cited references under 35 U.S.C. § 103(a). For the above reasons, as well as the reasons set forth in the Appeal Brief, Appellants respectfully request that the Board reverse the Examiner's rejections of all claims on Appeal. An early and favorable decision on the merits of this Appeal is respectfully requested.

Respectfully submitted,



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